Pharmacology Biochemistry and Behavior, Vol. 57, No. 4, pp. 863–868, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00321-8

Effect of Apomorphine on the Conflict-Induced Jumping Stereotypy in Bank Voles

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Received 13 April 1996; Accepted 16 August 1996

VANDEBROEK, I., AND F. O. ÖDBERG. *Effect of apomorphine on the conflict-induced jumping stereotypy in bank voles.* PHARMACOL. BIOCHEM. BEHAV. **57**(4) 863–868, 1997.—In conventional laboratory cages, bank voles (*Clethrionomys glareolus*) develop a jumping up-and-down stereotypy already before the age of one month. Central DA systems are thought to be involved in the expression of these conflict-induced stereotypies (CIS). Stereotypies can also be elicited pharmacologically, most commonly by amphetamine and apomorphine. Hence, administration of apomorphine to jumping bank voles provides the opportunity to compare pharmacologically-induced stereotypies (PHIS) and CIS in that species. A pilot study showed that apomorphine induced stereotyped licking that is qualitatively different from the CIS elicited by captivity. The present study investigated whether apomorphine has an effect on CIS-levels. The lowest dose (0.625 mg/kg) did not elicit licking but neither influenced jumping levels. Higher doses (0.938 and 1.094 mg/kg) lead to the occurence of licking but also suppressed CIS-levels. However, the discordance in time profiles of licking and jumping argues against a shift from jumping to licking due to further stimulation of already activated DA systems. Therefore, expression of jumping seems to depend on stimulation of other DA receptor subtypes or jumping may even be DA independent. © 1997 Elsevier Science Inc.

Stereotyped behaviour Captivity Dopamine Apomorphine Stress Jumping

STEREOTYPIES are characterized by a relatively invariant pattern, a regular repetition and apparent uselessness (16,20). According to the eliciting conditions they can be divided in pharmacologically-induced stereotypies (PHIS), conflict-induced stereotypies (CIS) and stereotypies that result from mental illness and some neurological disorders or trauma (24).

In rats and mice, PHIS are manifested as repetitive sniffing, licking, gnawing and limb movements (e.g. 1,3,4,9,28). PHIS are observed, amongst others, after administration of psychomotor stimulant drugs, such as apomorphine and amphetamine. When applied to animals, they are frequently used as a model for human psychiatric disorders, e.g. the amphetamine model for schizofrenia (22). It has been suggested that PHIS are mediated essentially by cerebral dopaminergic systems (7,23,26) although they can be elicited by drugs affecting other transmitter systems (for a review see 23).

Typical examples of CIS include chain-chewing in tethered sows, *Sus scrofa domestica* (5), spot-pecking in restricted-fed broiler breeders (25) and stereotyped walking in zoo-housed polar bears (33). Captive animals develop CIS in environments that are inadequate with regard to their species-specific needs. Captive bank voles (*Clethrionomys glareolus*) also frequently develop a characteristic jumping up-and-down stereotypy when raised in barren cages (population daily average number of jumps (n = 150): 6585; range: 3–45698 (18), already before the age of 1 month. The more active voles tend to show higher CIS-levels and vice versa, while voles that stop performing CIS also become less active in general (18,19).

It has been discussed before that CIS, as compared to PHIS, are a better functional animal model for studying similar symptoms in human psychoses and for the screening of potential psychotropic drugs (18,21). Furthermore, the use of CIS as welfare indicators to evaluate zootechnical life conditions of wild and domestic animals in captivity has been advocated by some authors (2,32). Others agree about their value as indicators, but point out that little is known about the extent of suffering as such (6,13).

The neurochemical mechanisms underlying CIS have not

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been as extensively studied as those of PHIS, probably because it is difficult to induce CIS in rats and most mouse strains (17,27). CIS in voles also seem to be mediated by cerebral dopaminergic systems (21). Furthermore, and even more important, the underlying neurochemical mechanism of those CIS appears to go through a developmental proces which enables to distinguish CIS younger than 4 months (developing stereotypies) from CIS older than 6 months (established stereotypies) (11).

In view of the possible involvement of cerebral DA systems, some authors reported increased CIS-levels after administration of dopamine agonists: *d*-amphetamine on rhythmic stereotypies in restriction reared chimpanzees (8), on route-tracing in caged canaries (10) and bromocriptine in high doses on object pecking in broiler breeders subjected to food restriction (12). Also, apomorphine administered to dogs provoked a stereotypy that resembled the CIS that develops under inadequate management conditions (15). However, previous work on CIS in voles (17) has shown that 2.50 and 1.25 mg/kg apomorphine elicited agitation and stereotyped licking (PHIS) while the jumping up-and-down stereotypy (CIS) was inhibited. The present study investigates whether the expression of PHIS or CIS depends solely upon the dose used or whether only PHIS are promoted by apomorphine. Therefore, a series of three doses of apomorphine lower than 1.25 mg/kg was tested.

MATERIALS AND METHODS

Animals

One male and one female were put together in transparent Makrolon cages (KOMECO type 375) with sawdust bedding filled with hay. After ±10 days the male was removed. Cotton wool was provided a few days before birth as nest material. All pups were born and bred in the same cage. At weaning (21 days), they were housed individually in similar but smaller cages (type 272) with sawdust bedding. Rodent pellets (Muracon G, Trouw, Belgium) and water were always available ad lib. The colony room was lit from 0900 until 2100 h. All voles used were older than 6 months (established stereotypies).

An example of the polyphasic activity cycle of bank voles is shown in Fig. 1. Peaks of activity lasting 1 to 4 h are separated by inactive periods of 1 to 6 h. The largest part of such peaks consists of CIS in stereotyping voles. Peaks can shift daily. They tend to be higher in the dark period. There is a considerable degree of inter- and intra-individual variation in duration of the active and inactive periods (18). The drug was administered when the natural activity level was subsiding and nearing its minimum level, hereby avoiding the possibility that increased CIS-levels were the consequence of the rising natural activity rather than apomorphine administration.

Drugs

Apomorphine hydrochloride (Federa, Brussels, Belgium) was diluted in NaCl 0.9% (w/v). Saline and drug solutions were pressure-sterilized (0.45 mm Sleicher & Schull membrane filter with a polysulfone membrane; Gelman Sciences, Michigan, USA). The solutions were administered SC (0.05 ml/10 g body weight) in the neck area.

Experimental Protocol

Detection of stereotyping and non-stereotyping voles. Ten stereotyping voles (age range 7–17 months) were selected from the colony by behavioural electronic recording and subsequent visual confirmation (18). The number of daily jumps was counted by photo-cells, while a general activity meter, positioned underneath each cage, registered all movements of each vole and allowed the monitoring of the activity rhythm. The height of the photo-cells discriminated between rearing and stereotyped jumping up-and-down. Other stereotypies than jumping can be electronically detected because they are accompanied by high general activity levels. Stereotyping and non-stereotyping individuals were defined as animals showing a daily average of more than 1000 and less than 500 photocell counts, respectively.

Experimental procedure. Apomorphine (0.625, 0.938 and 1.094 mg/kg) was administered in increasing dose to each animal. Due to the shift in the individual activity peaks, minimum one and maximum six days elapsed between the different doses. Because of the large inter-individual variability in stereotypy-level, a paired experimental set-up was chosen. Per observation session, two animals were injected blind, vole one with drug solution and vole two with saline and this was reversed 24 h later. The observation schedule is as follows: vole two is injected 2.5 min after vole one. Both voles are alternately observed during 2 min every 5 min for a total of 42 min (8 observation units for each vole until the end of the session). Maximum 4 pairs were tested daily, between 10 and 20 h.

Behavioural recording. The voles were visually observed with a Psion Organiser II LZ64 pocket computer loaded with the software packet "The Observer 2.0" (Noldus Information Technology, Wageningen, The Netherlands). An ethogram was generated including the following 11 behaviours (for a detailed description, except agitation and licking, see 18,19): 1. stereotyping: jumping up-and-down; 2. rearing; 3. grooming; 4. eating; 5. drinking; 6. sleeping; 7. immobility; 8. walking around while sniffing; 9. other behaviours: digging, gnawing, hanging and rooting; 10. agitation; 11. licking.

Agitation and licking are two behaviours induced in voles by apomorpine. Agitation is defined as spontaneously making wild jumps and/or nervously running throughout the cage, without pausing to sniff; licking as pulling the tongue fast in and out, eventually against an object.

Observation took place through a peep-hole (30 cm L × 3 cm W) in a wooden screen hiding the observer from the animals.

Data Analysis

Data are presented as the mean percentage of time each behavioural category was performed during a 2 min observation unit ± SEM (n = 10 individuals). Dose (0, 0.625, 0.938 and 1.094 mg/kg) and time (8 units: 5, 10, 15, 20, 25, 30, 35 and 40 min after injection) effects were investigated with a one-way ANOVA for repeated measures followed by post-hoc Student-Newman-Keuls test for multiple comparisons (α set at 0.05).

For the dose effect, mean values for the whole observation session and for the first and second 20 min post injection were calculated for each individual. ANOVA tests were always run on the raw data with three exceptions (immobility and walking during the second and licking during the first 20 min post-injection period), since normality testing failed. In those three cases transformation was applied prior to testing (log transformation for immobility and walking and square root transformation for licking; p-values for normality after transformation were 0.137, 0.056 and 0.056 respectively). Equal variance test-

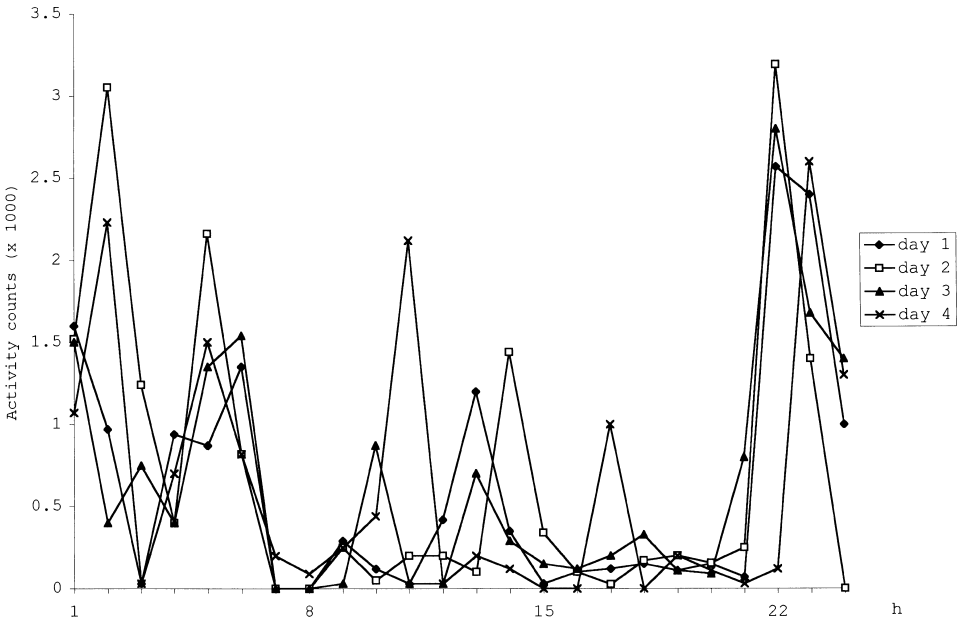

FIG. 1. A representative example of the polyphasic activity cycle of the bank vole. The time course of activity levels of one vole was recorded during four successive days by a general activity meter positioned underneath its cage.

ing never failed. The three saline sessions were pooled during further analysis since comparison revealed no significant differences for any of the behavioural measures.

For the time effect, square root transformation was performed on the raw data of the 8 observation units prior to testing.

Finally, Pearson product moment correlations were computed to examine the relation between the individual CIS-levels and the effect of each dose of apomorphine (expressed as the percentage decrease of CIS-levels relative to control values). The former was calculated as the mean percentage of time engaged in performing CIS during the entire observation session after injection with saline (average of the three controls). The effect of apomorphine was analysed for the whole session and for the first and the last 20 min. Two individuals had to be excluded from the latter test since they unexpectedly presented a very low CIS-level during the observations (2 and 3% respectively).

RESULTS

Effect of Apomorphine on CIS

Figure 2 shows the time course of CIS-levels after injection with saline or apomorphine. After each dose of apomorphine, there was an initial decrease of CIS-levels during the first 15 min, followed by a recovery to control levels (0.625 mg/kg), a sustained lower level (0.938 mg/kg) or a further partial inhibition (1.094 mg/kg). There was a time effect after 1.094 mg/kg ($F = 3.03$; $p = 0.008$), but not at lower doses ($F = 0.540$; $p = 0.801$ and $F = 1.07$; $p = 0.394$ for 0.625 and 0.938 mg/kg, respectively).

Table 1 summarizes the mean percentage of time voles spent performing the different behaviours after administration of saline or apomorphine during the whole observation and the session split into the first and the last 20 min. Behaviours that were not observed frequently enough for statistical analysis are not shown. This table reveals that up to 20 min after injection overall CIS-levels after apomorphine tend to be lower than the control values, although never significantly ($F = 1.43$; $p = 0.255$). However, during the last 20 min of the session, there is a dose-response relationship with increasing doses of apomorphine showing a greater inhibiting effect on CIS-levels ($F = 8.30$; $p = 0.001$). No correlation was found between basal CIS levels and the extent of apomorphine-induced inhibition of these CIS, except at the highest dose and only during the last 20 min ($r = 0.768$; $p = 0.026$).

PHIS Induced by Apomorphine

Licking was negligible after saline and 0.625 mg/kg apomorphine, but significantly increased after 1.094 mg/kg during the first 20 min (Table 1) ($F = 3.37$; $p = 0.033$).

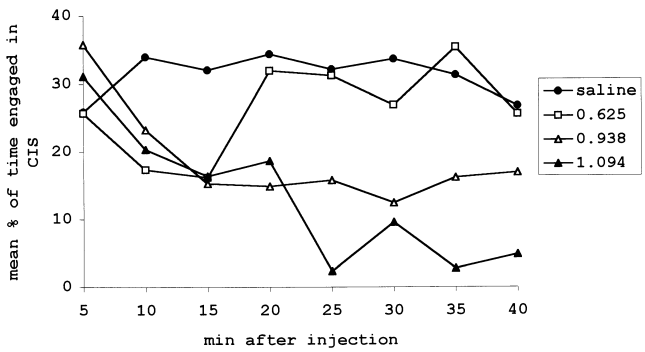

FIG. 2. Time course of the average CIS-level after injection with saline and the three doses of apomorphine (mg/kg) ($n = 10$).

TABLE 1

MEAN PERCENTAGE OF TIME ± SEM ENGAGED IN DIFFERENT BEHAVIOURAL CATEGORIES AFTER INJECTION WITH SALINE AND THREE DOSES OF APOMORPHINE (n = 10)

Behaviour Dose (mg/kg)	Total	First 20	Last 20
CIS			
Saline	31.3 ± 7.4	31.6 ± 8.0	31.0 ± 7.2
0.625	26.3 ± 6.0	22.8 ± 6.8	29.8 ± 7.4
0.938	18.8 ± 5.5[a]	22.3 ± 7.4	15.3 ± 4.6[a,b]
1.094	13.2 ± 3.2[a,b]	21.6 ± 6.3	4.8 ± 1.8[a,b]
Licking			
Saline	0.1 ± 0.0	0.1 ± 0.1	0.0 ± 0.0
0.625	0.4 ± 0.3	0.1 ± 0.1	0.0 ± 0.0
0.938	2.3 ± 2.1	4.6 ± 4.1	0.0 ± 0.0
1.094	3.0 ± 1.3	5.6 ± 2.5[a,b]	0.3 ± 0.2
Walk and sniff			
Saline	12.3 ± 1.3	14.1 ± 1.7	10.0 ± 1.3
0.625	19.4 ± 1.3[a]	23.4 ± 2.3[a]	15.5 ± 3.0
0.938	19.7 ± 2.3[a]	30.5 ± 3.6[a]	8.8 ± 2.1
1.094	23.8 ± 2.6[a]	36.1 ± 3.8[a,b]	11.4 ± 2.0
Rearing			
Saline	7.8 ± 1.3	7.9 ± 1.2	7.7 ± 1.4
0.625	8.7 ± 0.9	10.1 ± 1.3	7.3 ± 1.1
0.938	9.1 ± 1.5	12.3 ± 1.8[a]	6.0 ± 1.6
1.094	10.1 ± 1.2	15.3 ± 1.5[a,b]	4.8 ± 1.1
Grooming			
Saline	16.2 ± 1.8	16.5 ± 2.3	15.9 ± 2.3
0.625	11.3 ± 2.2	12.9 ± 3.2	9.6 ± 2.5
0.938	14.3 ± 1.8	18.5 ± 2.4	10.0 ± 3.3
1.094	14.1 ± 2.3	10.4 ± 2.9	17.8 ± 2.3
Immobility			
Saline	19.7 ± 4.3	23.4 ± 5.6	16.0 ± 3.6
0.625	25.6 ± 4.6	22.3 ± 5.8	28.9 ± 6.8[a]
0.938	18.3 ± 3.3	6.2 ± 1.7[a,b]	30.6 ± 5.7[a]
1.094	15.3 ± 2.4[b]	2.8 ± 1.1[a,b]	27.8 ± 4.3[a]
Eating			
Saline	2.9 ± 1.0	1.3 ± 0.9	4.6 ± 1.8
0.625	1.5 ± 0.8	0.8 ± 0.8	2.2 ± 1.2
0.938	4.1 ± 2.1	0.4 ± 0.3	7.7 ± 4.1
1.094	7.3 ± 2.2[a,b]	0.4 ± 0.3	14.2 ± 4.4[a,b]

[a] $p < 0.05$ versus control. [b] $p < 0.05$ versus 0.625 mg/kg.

Effect of Apomorphine on Other Behaviours

First half of the session. Walking around while sniffing was the only behaviour that was significantly increased by 0.625 mg/kg, other measured behaviours were unaffected (Table 1). Higher doses had a more pronounced effect: walking and rearing were dose-dependently increased, while immobility was dose-dependently decreased. Grooming was unaffected. Agitation was rare and observed exclusively during the first 20 min in 2, 3 and 4 out of ten animals with increasing doses (average values were 2.0, 5.0 and 4.2 s, respectively).

Last half of the session. After 0.625 mg/kg, immobility was the only behaviour affected. It was increased by 80% as compared to saline. This behaviour was increased to the same extent with higher doses. Walking around while sniffing, rearing and grooming were unaffected. Eating was significantly increased by the highest dose ($F = 5.14$; $p = 0.006$) (Table 1).

DISCUSSION

Data from a previous experiment (17) showed that levels of stereotyped jumping up-and-down (CIS) in voles were not increased with 2.50 and 1.25 mg/kg apomorphine. On the contrary, these doses inhibited CIS and induced stereotyped licking (PHIS) and agitation. We wondered whether CIS-levels could be increased by doses that did not yet elicit this oral stereotypy. Therefore, this study investigated the acute effect of doses lower than 1.25 mg/kg on CIS-levels of bank voles.

The present results demonstrate that after administration of 0.625 mg/kg apomorphine licking and agitation were not induced, nor was there an effect on CIS-levels. After 0.938 and 1.094 mg/kg, CIS-levels initially tended to decrease relative to controls and licking was scantily induced. This lower CIS-level was either sustained (0.938 mg/kg) or further partially inhibited (1.094 mg/kg) during the second 20 min post-injection period.

These results are in agreement with a study in pigs, in which the effects of different doses of apomorphine (0–1.0 mg/kg) were compared. The behavioural syndrome elicited by apomorphine differed qualitatively from the CIS expressed by this species under restrictive feeding and housing conditions (29). Furthermore, levels of PHIS elicited by a standard dose of amphetamine before a period of physical restraint and restrictive feeding were negatively correlated with levels of CIS that developed during the restrictive housing treatment (30).

There is the question of whether pharmacological stimulation of DA receptors with apomorphine has additive effects on the behaviour of jumping voles. It is known that some behaviours are associated with the performance of CIS. Stereotyping voles show lower levels of immobility and higher levels of walking and rearing as compared to non-stereotyping ones. Intra-individually, walking and rearing decrease and immobility increases when stereotyping voles stop performing their CIS (19). In the present study, the lowest dose of apomorphine stimulated walking during the first 20 min after injection. Higher doses increased rearing as well as walking, decreased immobility and induced scantily stereotyped licking. Thus, in spite of the activation by apomorphine of behavioural patterns which are normally associated with the performance of CIS in drug-free voles, stereotyped licking was promoted instead of jumping. One could wonder whether this is due to the fact that licking represents a higher hierarchical level than jumping regarding dopaminergic activity, as has been demonstrated in the rat (9): increasing doses of apomorphine resulted in a shift from sniffing to licking and subsequently to gnawing. However, in the present study, licking was dose-dependently induced and the 30% decrease in CIS-levels was not significantly different from controls in the first 20 min. A dose-dependent decrease in jumping only occured during the last 20 min. Therefore, the discordance in time profiles between licking and jumping argues against a reduction of jumping due to a shift to licking.

It is also unlikely that general sedation is the cause of the dose-dependent decrease in CIS-levels during the last 20 min. Inhibition of stereotypies, measured as percentage of time, must inevitably be reflected by increases elsewhere. However, there is little evidence in this experiment to suggest general inhibition because other forms of motor activity, such as walking and rearing, were unaffected. Moreover, although immo-

bility was significantly increased as compared to saline, there was no dose-dependent elevation of this increase. Furthermore, levels of immobility were already significantly elevated after the lowest dose while no effect on jumping levels was observed. The only other behaviour that is significantly increased during the last 20 min is eating. However, this does not explain the significant decrease in jumping levels at the intermediate dose since eating is only significantly increased after the highest dose. Therefore, jumping is probably not decreased due to behavioural competition with eating.

Two explanations can be put forward. First, since apomorphine has a different affinity and selectivity for the different subclasses of DA receptors than DA it may be possible that jumping depends upon stimulation of other DA receptor subtypes than those that are activated by apomorphine. Focusing on dopamine receptor subtypes, as has been done for PHIS (31) and for oral CIS in restricted-fed fowls (12), will allow perhaps to distinguish between PHIS and some types of CIS on the one hand and provide new insights in the neurobiochemical mechanisms underlying different types of CIS on the other. In addition, *in vivo* microdialysis sampling in dopamine containing brain loci of respectively stereotyping and non-stereotyping bank voles could clarify the contribution of the different dopaminergic pathways in the jumping stereotypy.

Alternatively, it may be true that the expression of captivity-induced jumping is DA independent. Indeed, the fact that average daily CIS-levels were increased, partially inhibited and unaffected by repeated administration of respectively L-DOPA, α-methyl-para-tyrosine (a tyrosine-hydroxylase inhibitor) and fusaric acid (a potent noncompetitive inhibitor of dopamine-β-hydroxylase) (21) does not rule out this possibility. Interestingly, although repeated administration of 0.2 mg/kg haloperidol, a predominantly D_2-antagonist that is also known to inhibit DA-agonist induced stereotypies (14), was able to selectively decrease average daily jumping levels (11), the same dose failed to do so in an acute experiment (17). However, this sole observation is not sufficient to confirm the hypothesis of DA-independence. Conducting acute experiments with various selective DA-antagonists and with irreversible DA-blockade would therefore be an important follow-up.

In summary, the results of the present study show that levels of stereotyped jumping up-and-down induced by a restrictive and monotonous environment (CIS) in bank voles cannot be increased by apomorphine. A dose that does not yet elicit stereotyped licking (PHIS) has no effect on CIS-levels, while gradually increasing the dose leads to the occurence of PHIS. These results seem to suggest that other subtypes of DA-receptors are involved in the expression of jumping or that jumping may even be DA-independent.

ACKNOWLEDGEMENTS

This research was supported by a specialization grant of the Flemish Institute for the Promotion of Scientific-Technological Research in Industry (IWT). Many thanks are due to Prof. Dr. Norbert Fraeyman for critical reading of the manuscript and for stimulating discussions.

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